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Gram-Scale Synthesis of Iejimalide B

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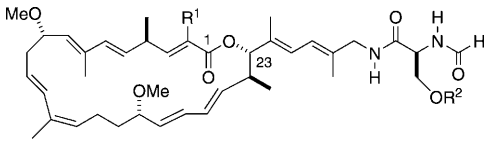
Abstract: Iejimalide B (**2**) is the most promising member of a small family of marine polyene macrolides endowed with remarkably selective activity against human cancer cell lines. As this product, however, is hardly available from the natural sources, a detailed evaluation requires the development of an efficient and practical synthetic approach. This challenge has now been met by adapting the first total synthesis of **2** previously reported by our group to the needs of high material throughput. Redesigning the access routes to the five required building blocks in combination with a careful optimization of the fragment coupling processes provided gram amounts of this valuable compound in a sequence of no more than 16 linear steps with an overall yield of about 7%. Key elements of the successful strategy include: i) three hydrostannylation processes of elaborate terminal alkynes with "lower order" stannyl cuprates, ii) a Brown allylation, a Noyori transfer hydrogenation, and a Marshall propargylation to set the chiral centers at C9, C17, C22 and C23, and iii) a modified Takai–Utimoto olefination for the preparation of the very labile skipped 1,4-diene flanking the ester group. The assembly process benefited from a particularly mild protocol for the Stille cross-coupling previously developed in this laboratory, which clearly outperformed the alternative Suzuki reaction in terms of yield and scalability. The 24-membered macrocyclic frame was forged by a remarkably selective ring-closing metathesis reaction (RCM), in which two out of the ten double bonds present in the cyclization precursor were selectively activated with the aid of a second-generation Grubbs catalyst.

Keywords: asymmetric catalysis · cross-coupling · metathesis · natural products · total synthesis

Introduction

In 1988, Kobayashi and co-workers reported the isolation of the polyene macrolides of the iejimalide family (**1**–**4**) from the marine tunicate *Eudistoma* cf. *rigida* collected off Ie island in the Okinawa archipelago.[1] The proposed constitution of these extremely scarce secondary metabolites (0.003–0.006% of the tunicates wet weight) was corrected and their stereostructure established only 15 years later after a re-extraction from a *Cystodytes* sp.[2] Although more recent data suggest that these compounds might actually be produced by symbiotic cyanobacteria rather than the tunicates themselves,[3] the very limited supply of **1**–**4** from the natural sources severely hampered a detailed biological evaluation. As the original publication had only shown cytotoxicity against two murine leukemia cell lines,[1] the promising activity of the iejimalides against a multitude of human cancer cell lines in vitro transpired only after the re-isolation campaign had enabled a more detailed screening.[2b,4] These studies also indicated a lack of homology between the selectivity profile of the iejimalides and the recorded anticancer agents in the NCI database.[5] Remarkably, Kobayashi et al. also claimed in vivo efficacy of **3** and **4** against P388 leukemia in mice at doses of 200 $\mu g\,kg^{-1}\,d^{-1}$.[2b]



Iejimalide A (**1**): $R^1 = R^2 = H$
Iejimalide B (**2**): $R^1 = Me$, $R^2 = H$
Iejimalide C (**3**): $R^1 = H$, $R^2 = SO_3Na$
Iejimalide D (**4**): $R^1 = Me$, $R^2 = SO_3Na$

The mechanism of action responsible for the promising cytotoxicity of the iejimalides remains to be fully investigated. Yet, the available information suggests that V-ATPases are one of the relevant biological targets,[6,7] which might also explain the reported anti-osteoporotic activity of **1**–**4**.[8] Depending on the particular cell type, these macrolides cause cell cycle arrest, induce apoptosis, and modulate the steady state level of several gene products associated with cell cycle progression and cell death.[9,10] Furthermore, it has been shown that their cytotoxicity is not caused by tubulin binding, whereas the actin cytoskeleton of fibroblast cells is strongly perturbed upon incubation with micromolar concentrations of iejimalide B and analogues.[10]

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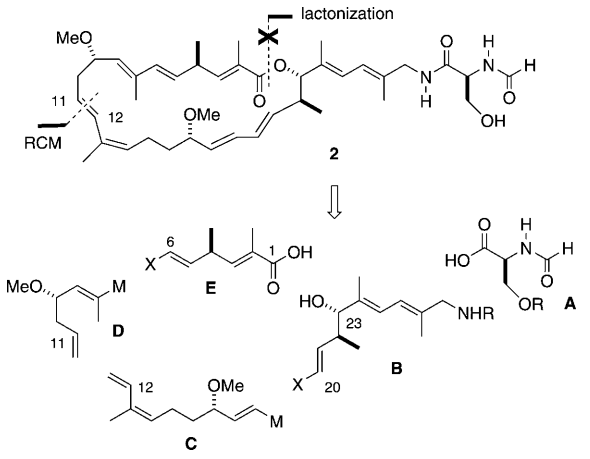
The first total synthesis of all naturally occurring iejimalides reported by our group provided sufficient amounts of these valuable compounds for an independent biological evaluation.[10–12] The promising results obtained in the first round encouraged us to perform a more detailed screening; this extended program did not only rely on various cell-based assays, but also included colony-based assays using experimental tumors as well as in vivo testing in mice against selected human cancer xenografts.[13] As such a campaign, however, mandates a secured material supply, a truly practical and scalable synthesis of iejimalide B (**2**) as the most promising member of the series had to be devised. Given the potency of **2**, we arbitrarily targeted one gram of this particular compound; the chemistry that enabled us to reach this goal is outlined below. At the same time, our endeavor at the chemistry/biology interface was also intended to lay a solid basis for a synthesis-driven exploration of the structural space surrounding the natural products themselves.[14] This second part of our agenda, together with details concerning the biological activities of the iejimalides and a panel of non-natural analogues, is disclosed in the accompanying paper.[13]

Results and Discussion

Synthesis plan and strategic considerations: Our initial analysis had dissected the iejimalide structure into five building blocks **A**–**E** of similar size and complexity, which allow the molecular frame to be assembled in a highly convergent manner (Scheme 1).[10,11] The flexibility of this plan paid dividends when the originally intended macrolactonization for the formation of the 24-membered core essentially met with failure.[11a,15] Without undue preparative efforts, the assembly process could be re-programmed toward macrocyclization by ring-closing metathesis (RCM)[16] at the C11–C12 bond. Even though this tactics required selective activation of two out of ten olefins in the metathesis precursor with the aid of a Grubbs-type catalyst, we were pleased to find that this risky maneuver opened access to **2** and congeners.[10,11b] It is also obvious that the overall strategy is well suited for the synthesis of analogues by introducing the desired structural "point-mutations" into one or more of the parent fragments **A**–**E**. In view of these inherent advantages, the basic synthesis blueprint was kept unchanged during the up-scaling campaign.



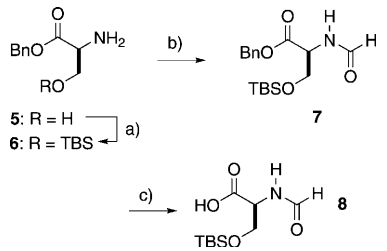
Scheme 1. Disconnection of **2** into five building blocks of similar size and complexity.

Yet, we had learned during our early work that several intermediates en route to **2** are unusually sensitive toward acid, base and gentle warming; moreover, facile double-bond isomerizations in the presence of even weak nucleophiles had plagued the preparation of fragments **C** and **E**. Although these difficulties could ultimately be mastered,[10,11] it was clear that each building block and all fragment coupling processes needed scrupulous reinvestigation for larger-scale material throughput.

The *N*-formylserine segment: The tail of the iejimalides terminates in an *N*-formylserine moiety, which imparts significant polarity onto the compounds despite of their apolar cores. Sulfatation of the primary hydroxyl group, as displayed by iejimalide C (**3**) and D (**4**), increases the polar character even further.[1,2]

Although the preparation of the required building block **A** follows established procedures of peptide chemistry, careful compliance with the optimized reaction conditions is mandatory because of the proclivity of *N*-formylserine derivatives toward racemization, formyl cleavage and oxazoline formation (Scheme 2). In fact, even gentle warming of the reaction mixture upon O-TBS protection of the hydroxyl group of commercial benzyl serinate **5** may cause partial or complete racemization within short periods of time. No such problems, however, were encountered when the silylation was performed at ambient temperature (*ee* $\geq$99%, 6.7 g scale).[17] In this context it is of note that the rotatory power of **6** is strongly concentration dependent; therefore it is advisable to check the optical purity of the material by HPLC.

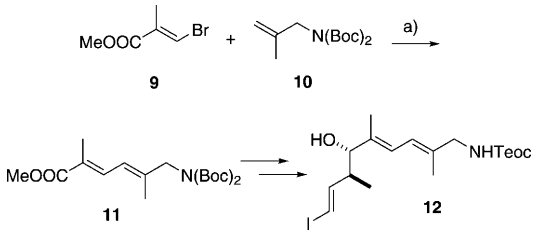
Whereas a literature procedure employs trifluoroethoxy formate in the formylation step,[18] we found the use of cheap formic acid in combination with EDC and catalytic amounts of DMAP much more practical. The resulting



Scheme 2. a) TBSCl, DBU, MeCN, 0°C→RT, quant.; b) EDC·HCl, DMAP, HCOOH, 0°C → RT, 94%, >98% *ee*; c) H_2 (1 atm), Pd/C cat., EtOAc, MeOH, 98%; DMAP = 4-dimethylaminopyridine, EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbonyldiimide, TBS = *tert*-butyldimethylsilyl.

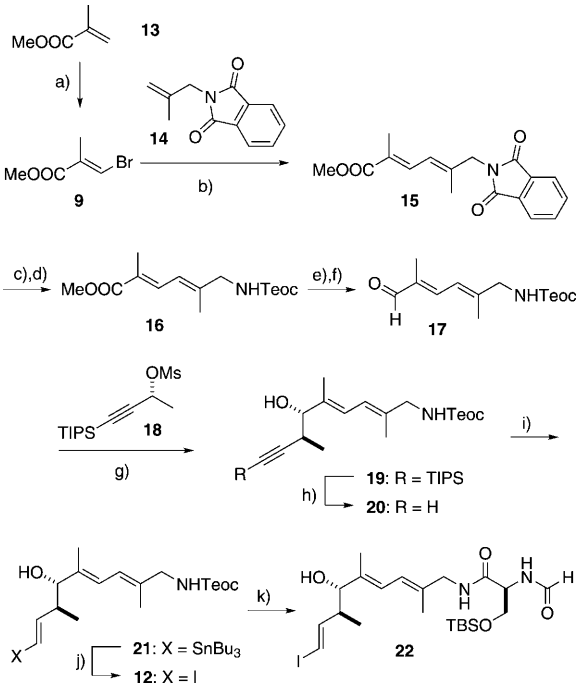
product **7** was obtained in 94% yield on a 6.8 g scale with an uncompromised *ee* of 98–99%. The final hydrogenolysis of the benzyl ester over palladium on charcoal was best performed in a mixed solvent system comprising EtOAc and MeOH to avoid precipitation of the resulting acid **8**, which may occlude the catalyst and hence cause the reaction to cease.[19]

The tail region: Since the preparation of the Eastern segment **B** defines the longest linear sequence of the total synthesis and therefore determines the overall yield, particular care was paid to the optimization of all individual steps. The original route, though quite efficient, was not considered satisfactory in practical terms (Scheme 3). Although the initial Heck coupling of **9** with **10** gave yields of up to 84%,[10] the reproducibility of the reaction on larger scale was poor. Moreover, the need for two N-Boc substituents, which had to be removed in a stepwise fashion later in the sequence, is deemed inappropriate with regard to step count and atom economy.[20,21]



Scheme 3. Original route to a key intermediate representing synthon **B**: a) $Pd(OAc)_2$ (3 mol%), P(*o*-tolyl)$_3$ (6 mol%), Et_3N, 100°C, up to 84%, cf. ref. [10].

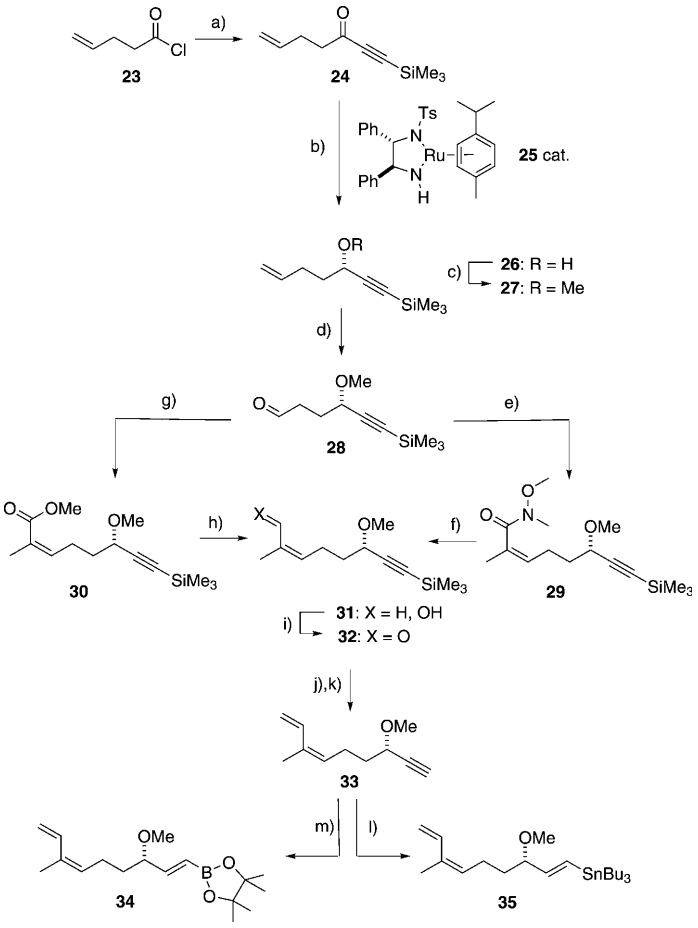
A very convenient alternative was found with phthalimide **14**, which is readily available by standard N-alkylation (91%, >90 g scale) (Scheme 4). A palladium-catalyzed Heck reaction[22] with bromide **9**, for which an expedient two-step/one-pot preparation was devised (92% overall, 100 g scale), gave diene **15** in well reproducible yields of 68% on a 50 gram scale. As the product can be collected by crystallization from the crude mixture, a further up-scaling of this transformation should be straightforward. Cleavage of the phthalimide with methylamine[23] followed by introduction of an N-Teoc group,[24] which had previously turned out advantageous in the downstream Marshall propargylation,[25] provided multigram amounts of **16** (11.1 g, single largest batch) after the first flash chromatography necessary during this route. Adjustment of the oxidation state gave aldehyde **17** without difficulties, which was subjected to a palladium-catalyzed, zinc-induced reaction with propargyl mesylate **18** carrying a bulky TIPS group at the alkyne terminus. This large substituent renders the Marshall propargylation highly diastereoselective,[26] furnishing the *anti*-configured compound **19** in pure form in 70% yield on a >10 gram scale.[27]



Scheme 4. a) Br_2, CH_2Cl_2, 0°C, then DBU, 0°C → RT, 92%; b) $Pd(OAc)_2$ (2.5 mol%), P(*o*-tolyl)$_3$ (5 mol%), Et_3N, 100°C, 68%; c) $MeNH_2$, EtOH; d) 4-$O_2NC_6H_4$-O-C(O)-$OCH_2CH_2SiMe_3$, Et_3N, CH_2Cl_2, 85% (over both steps); e) Dibal-H, CH_2Cl_2, −78°C, 86%; f) MnO_2, CH_2Cl_2; g) $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), Et_2Zn, THF, −78°C → RT, 70% (over both steps); h) TBAF, THF, 0°C, 87%; i) $(Bu_3Sn)_2$, BuLi, THF, CuCN, −78°C → RT, then **20**, −78°C, 95%; j) I_2, Et_2O, 0°C → RT, 90%; k) (i) Et_4NF, MeCN, 40°C; (ii) **8**, HOBt, EDC·HCl, *N*-methylmorpholine, CH_2Cl_2, 90% (over two steps). HOBt = 1-hydroxy-1*H*-benzotriazole, TBAF = tetra-*n*-butylammonium fluoride; Teoc = 2-(trimethylsilyl)-ethoxycarbonyl.

After the removal of the C-silyl group with TBAF in THF at low temperature to avoid premature cleavage of the N-Teoc substituent, various options for the further elaboration of the resulting product **20** were explored. Although the original route involving temporary protection of the hydroxyl group as a pivalate ester followed by hydrozirconation/iodination of the terminal alkyne scaled well,[10] stannylcupration of **20** followed by iodine for tin exchange (**21** → **12**) constitutes a superior alternative. It circumvents problems caused by variable qualities of commercial $[Cp_2Zr(H)Cl]$ and is less expensive; moreover, the protection/deprotection of the alcohol group is avoided, thus reducing the step count. Careful optimization of the reaction conditions showed that the use of the "lower-order" stannyl cuprate generated from Bu_3SnCu and LiCN in THF at ambient temperature gave optimal results.[28] Under these conditions, excellent yields and selectivities were secured (95%, >3 g scale, *E*/*Z* >30:1), whereas the same reaction, when performed at −78°C, resulted in a 1:1 mixture of double bond isomers. Cleavage of the Teoc-group in **12** followed by introduction of the *N*-formylserine moiety with the aid of EDC and HOBt readily provided gram amounts of the "Eastern" segment **22** (1.15 g, single largest batch) in readiness for fragment coupling.

Elaboration of the Southern sector: Commercial 4-pentenoic acid chloride (**23**) was selected as point of departure for the preparation of the required coupling partner, as it reacted cleanly with bis-trimethylsilylacetylene in the presence of $AlCl_3$ (Scheme 5); the resulting ketone **24** could be conveniently purified by Kugelrohr distillation (83%, >16 g).[29] The subsequent transfer hydrogenation under Noyori's conditions also worked admirably well, furnishing propargyl alcohol **26** in 98% yield (>8 g scale) and 98.8% *ee*, provided that the isopropanol serving as the reductant and the solvent was carefully degassed.[30] As previously mentioned, however, the seemingly routine O-methylation of the secondary hydroxyl group in **26** required careful optimization.[10] Best results were obtained using *n*BuLi in THF as the base and DMSO as an aprotic dipolar cosolvent.[29] Under these conditions, good reproducibility and a high yield of **27** were secured when working on a multigram scale.



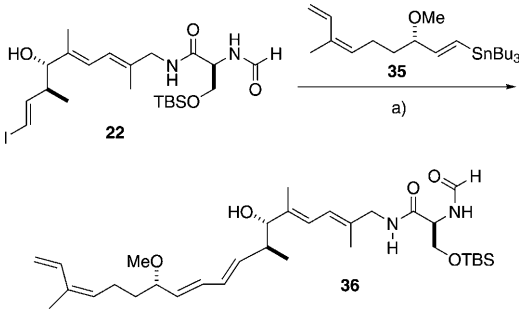
Scheme 5. a) $Me_3SiC{\equiv}CSiMe_3$, $AlCl_3$, 0°C → 20°C, 83%; b) **25** (0.6 mol%), *i*PrOH, 98%, 98.8% *ee*; c) BuLi, THF, −78°C, then DMSO, MeI, −25°C → RT, 99%; d) O_3, Sudan red 7B cat., then PPh_3, 92%; e) $(F_3CCH_2O)_2P(O)CH(Me)CON(OMe)(Me)$,[33] [18]crown-6, KHMDS, THF, −78°C, 72% (*E*/*Z* 1:11); f) Dibal-H, CH_2Cl_2, −78°C, 63% (*E*/*Z* ≈3:1); g) $(F_3CCH_2O)_2P(O)CH(Me)COOMe$, KHMDS, [18]crown-6 (0.8 equiv), THF, −78°C, 85%; h) Dibal-H, CH_2Cl_2, −78°C; i) TEMPO (20 mol%), Bu_4NCl (20 mol%), NCS, CH_2Cl_2, aq. phosphate buffer (pH 8.6); j) $Ph_3P{=}CH_2$, THF, −78°C; k) K_2CO_3, MeOH, 71% (over steps h)–k)); l) $(Bu_3Sn)_2$, BuLi, CuCN, −78°C → RT, then **33**, −78°C, 81%; m) pinacolborane, 9-H-9-BBN (10 mol%), THF, 45°C, 56%; TEMPO = 2,2,6,6-tetramethyl-1-piperinyloxy; NCS = *N*-chlorosuccinimide.

Next, we were committed to improve the selective cleavage of the double bond in **27** in the presence of the alkyne, which had relied on the use of OsO_4 (10 mol%) in combination with $NaIO_4$ and 2,6-lutidine in the original total synthesis.[10] After some experimentation it was found that ozonolysis in MeOH is a much better solution, provided that the reaction was monitored by the use of Sudan red 7B as an indicator.[31,32] This dye decolorizes once the alkene has been completely consumed; therefore the reaction can be stopped in time to avoid any over-oxidation of the alkyne unit. This reliable protocol allowed for significant material throughput.

Two different variants for the elaboration of the aldehyde group in **28** into the required terminal 1,3-diene moiety were investigated. However, the shorter route via Weinreb amide **29**[34] turned out to be troublesome because of partial isomerization of the (*Z*)-configured trisubstituted alkene during the reduction with either Dibal-H or $LiAlH_4$. This step was much cleaner with the corresponding ester **30**, which was prepared as a single isomer by a modified Still–Gennari olefination[35] employing only substoichiometric amounts of [18]crown-6 as additive.[36] The use of either toluene or THF gave similar results, but the isolation of the somewhat volatile product was easier with the latter solvent (85%, >7 g scale). Reduction of **30** with Dibal-H followed by oxidation of the resulting allylic alcohol **31** furnished aldehyde **32**. Although the use of excess MnO_2 is effective for this purpose, problems with partial isomerization of the α,β-unsaturated system were occasionally observed. This undesirable process could be largely avoided by recourse to catalytic TEMPO in combination with NCS as the final oxidant in a biphasic CH_2Cl_2/buffer medium (*Z*/*E* >20:1 in all cases investigated).[37,38] **32** was immediately subjected to a Wittig olefination with preformed $Ph_3P{=}CH_2$ followed by desilylation of the resulting product with K_2CO_3 in MeOH. From the practical viewpoint it is important to note that the four operations, by which enoate **30** was converted into diene **33**, did not mandate rigorous purification of the intermediates and therefore gave a satisfactory 71% overall yield after a single flash chromatography.

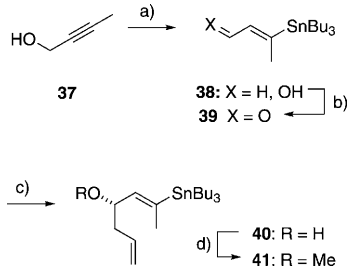
A chemoselective hydrometalation of the alkyne in the presence of the 1,3-diene transforms compound **33** into the required building block in readiness for fragment coupling with alkenyl iodide **22**. Although hydroboration with pinacol borane, entrained by the addition of catalytic amounts of 9-H-9-BBN,[39] gave acceptable yields in reactions using ≤500 mg of substrate,[10] the transformation was erratic upon further scale-up. Gratifyingly, however, stannylcupration of **33** with the lower order cyanocuprate formed from Bu_3SnCu and LiCN,[28] which had already worked exquisitely well during the advancement of Marshall-adduct **20** to alkenyl iodide **22**, was found clearly superior in terms of yield and scalability. Moreover, the subsequent fragment coupling of the resulting stannane **35** with alkenyl iodide **22**, when performed according to the Stille protocol previously devel-

oped by our group for challenging cases,[40–42] secured gram amounts of the fully functional Southern sector **36** in well reproducible 87% yield (1.3 g, single largest batch) (Scheme 6). This result clearly exceeds the outcome of the competing Suzuki reaction[43] between boronate **34** and iodide **22**, which delivered the same product in only 66% yield, even though the conditions had previously been carefully optimized.[10] We tentatively ascribe the superior performance of the Stille coupling to the fact that the used cocktail of catalytic $[Pd(PPh_3)_4]$, copper thiophenecarboxylate (CuTC), and $Ph_2PO_2NBu_4$ in DMF ensures particularly mild and essentially neutral conditions, and is therefore well suited for delicate bond-forming reactions as is the case with the heat- and base-sensitive polyene **36**.[40,41] The fluoride-free and essentially neutral conditions ensure compatibility of this method with the primary -OTBS ether and preclude epimerization of the racemization-prone *N*-formyl serine residue.



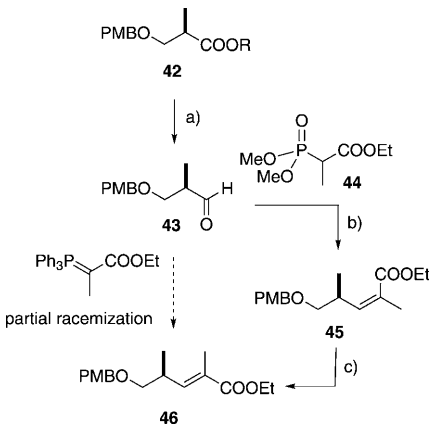
Scheme 6. a) $[Pd(PPh_3)_4]$ (4 mol%), $[Ph_2PO_2][NBu_4]$, CuTC, DMF, 87%; CuTC = copper thiophene-2-carboxylate.

Evolution of a practical synthesis of the acid perimeter: Although the large-scale synthesis of segment **D** followed our previous route, the procedures were partly modified to enable high material throughput (Scheme 7). Most notably, the first step of the sequence became more reliable upon replacement of the "higher-order" stannyl cuprate generated from $[Bu_3Sn(Bu)Cu]Li$ and LiCN, which had been recommended in the literature and was therefore used in our original approach,[44] by the "lower-order" stannyl cuprate derived from Bu_3SnCu and LiCN (see above).[28] Respectable amounts of compound **38** became available in excellent yield and purity by this modification (86%, >8.3 g scale), which was subjected to allylic oxidation with MnO_2. To this end, it was beneficial to use a large excess of the oxidant, as shorter reaction times generally furnished purer product.[45] The resulting aldehyde **39** then underwent a productive Brown allylation under salt-free conditions[46] to give alcohol **40** in essentially quantitative yield and excellent optical purity (95% *ee*, HPLC), which was methylated on exposure to Meerwein salt in the presence of proton sponge as the optimal base. Overall, this four-step sequence secured generous amounts of compound **41** as a surrogate of building block **D** (71% overall, >6 g single largest batch).



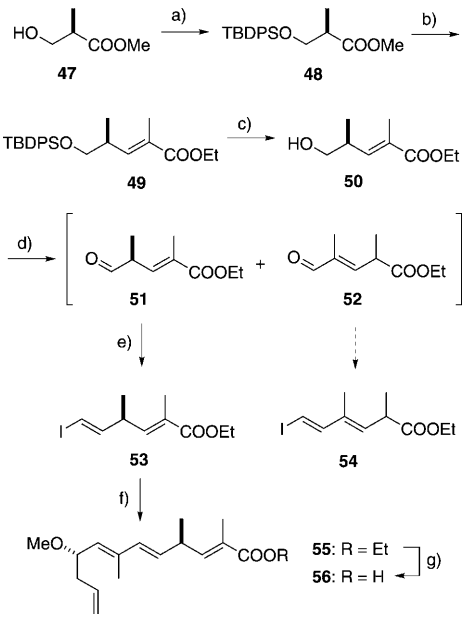
Scheme 7. a) $(Bu_3Sn)_2$, BuLi, THF, CuCN, −78°C → RT, then **37**, −78°C, 86%; b) MnO_2, CH_2Cl_2, 88%; c) (−)-$Ipc_2BCH_2CH{=}CH_2$, Et_2O, −100°C, 99%, 95% *ee*; d) $[Me_3O]^+$ $[BF_4]^-$, proton sponge, CH_2Cl_2, 0°C → RT, 95%. Ipc = isopinocampheyl.

A significant improvement in the preparation of the second northern subunit **E** hinged upon the proper choice of a single protecting group. Our original approach (Scheme 8) had started with the PMB-protected Roche ester derivative **42**, which did not provide access to the required intermediate **46** by reduction/Wittig olefination because of serious racemization of the chiral center under the chosen conditions (<55% *ee* of **46**).[10] Therefore we had to run a Horner–Emmons olefination of the derived aldehyde **43** with phosphonate **44** at low temperature, which delivered the enoate **45** in acceptable optical purity (≥92% *ee*), albeit as the unwanted *Z* isomer. This outcome could be corrected by treatment of **45** with PhSSPh and AIBN, but the long reaction time (96 h) and necessary high loading of the radical initiator were far from optimal.[10]



Scheme 8. Original approach toward segment **E**: a) Dibal-H, CH_2Cl_2, −78°C; b) **44**, LiHMDS, THF, −78°C → −40°C; c) PhSSPh, AIBN, THF, reflux, 77% (over three steps, E/Z = 20:1), cf. ref. [10].

Following a lead from the work of Ley and co-workers,[47] who did not report any problems with racemization when working with the analogous Roche ester derivative **48** carrying a bulky TBDPS-ether, the sequence of Dibal-H reduction followed by conventional Wittig olefination with freshly prepared $Ph_3P{=}C(Me)COOEt$ was reinvestigated (Scheme 9). We were pleased to note that this simple



Scheme 9. a) TBDPSCl, imidazole, DMAP cat., CH_2Cl_2, 90%, cf. ref. [48]; b) (i) Dibal-H, hexane, −78°C; (ii) $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2, 82%; c) TBAF, THF, 0°C → RT, 86%; d) TEMPO (1 mol%), KBr, NaOCl, CH_2Cl_2, aq. phosphate buffer (pH 7.4); e) $CrCl_2(THF)_{1.8}$, THF/1,4-dioxane, CHI_3, then **51**, 59% (over both steps); f) **41**, $[Pd(PPh_3)_4]$ (4 mol%), $[Ph_2PO_2][NBu_4]$, CuTC, DMF, 84%; g) aq. LiOH, MeOH, THF, 80%. TBDPS = *tert*-butyldiphenylsilyl.

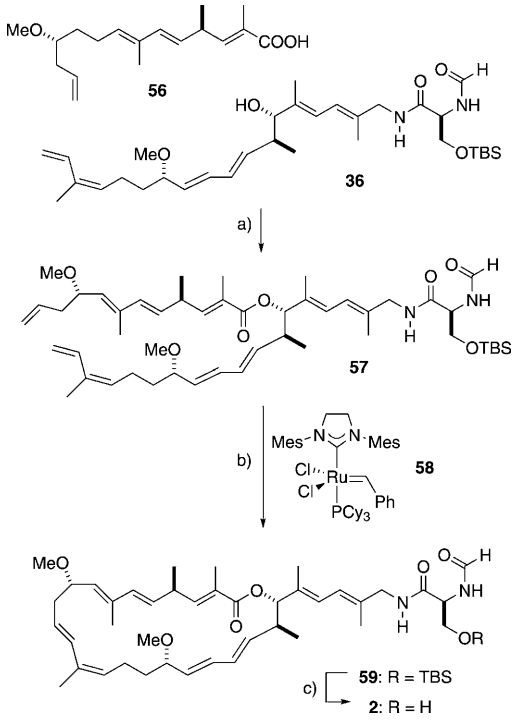
change furnished product **50** with >99% *ee* after cleavage of the silyl group.

With multigram amounts of optically pure alcohol **50** in hand, we were in the position to study the crucial oxidation to aldehyde **51** in greater depth, which was arguably one of the most delicate operations in the original synthesis.[10] As expected, **51** is exceptionally sensitive since the double bond can migrate from conjugation to the ester into conjugation to the aldehyde (in **52**). This bias was previously experienced when **51** was prepared with Dess–Martin periodinane[49] with or without addition of various amounts of bases to neutralize possible traces of acid in the medium. As the crude aldehyde was immediately subjected to a subsequent Takai–Utimoto olefination,[50,51] the required alkenyl iodide **53** was invariably obtained as a mixture with the undesired diene **54**, which could not be separated by flash chromatography at this stage.[52] Only after the subsequent Stille reaction with alkenyl stannane **41** and saponification of the ester groups in the resulting products were we able to obtain acid **56** in acceptable purity, which represents the northern sector of iejimalide B.[10]

After considerable experimentation it was found that the use of catalytic TEMPO in combination with NaOCl in buffered medium (pH 7.4)[53] allowed aldehyde **51** to be prepared in isomerically pure form. The reaction was repeated several times and found well reproducible on different scales. This aldehyde, however, must be processed without delay to the corresponding alkenyl iodide **53** by a Takai–Utimoto olefination. Despite the excellent track record of this transformation,[51] partial isomerization of the double bond could not be suppressed when the reaction was performed under the standard conditions. However, this problem was circumvented by a modification which we believe might be beneficial in other challenging cases too. Whereas Takai–Utimoto olefinations are usually carried out under "Barbier-type" conditions by mixing the aldehyde, CHI_3 and the appropriate amount of $CrCl_2$ in an ethereal solvent,[54] we found it possible and advantageous to form the intermediate chromium carbenoid reagent *prior* to the addition of the carbonyl partner.[55] To this end, CHI_3 and $CrCl_2$ were stirred in THF/1,4-dioxane (1:6) at ambient temperature before a solution of isomerically pure aldehyde **51** in dioxane was introduced. Under these conditions, the olefination proceeded very fast and cleanly, delivering the desired alkenyl iodide **53** with excellent E selectivity ($E/Z > 20{:}1$); only traces of isomeric compounds were detected in the crude mixture, and **53** was isolated in pure form in an appreciable 59% yield over two steps (Scheme 9). In practical terms, the preparation of the chromium carbenoid derived from CHI_3 and the TEMPO oxidation of alcohol **51** were best performed in parallel; since the oxidation (15 min) as well as the olefination step (30 min) both proceed rapidly, significant amounts of material can be quickly brought through, even though the largest batch of **53** produced in this way was restricted to one gram of product. As expected, the reaction of this iodide with stannane **41**, using again the three-component cocktail (Pd^0, CuTC, $Ph_2PO_2NBu_4$) previously described by our group,[40,41] proceeded smoothly, as did the final saponification of the ethyl ester in **55** under standard conditions. Overall, the modifications outlined above secured an excellent supply of the acid perimeter **56** as required for the gram scale total synthesis of iejimalide B.

Completion of the total synthesis: Our previous experiences[11a] together with complementary results from the literature[15] taught us that the seemingly routine esterification of the acid fragment **56** with the allylic alcohol **36** is far from trivial. The labile nature of both reaction partners, the steric hindrance of the alcohol group, and the peculiarities of a skipped α,β,δ,ε-unsaturated acid component collectively account for the difficulties previously encountered. Not surprisingly therefore, this step required serious study during the up-scaling campaign.

After extensive screening and careful optimization, it was found that ester **57** was formed in well reproducible 82% yield with EDC·HCl as the activating agent, provided that the following conditions were scrupulously met (Scheme 10): acid **56**, the activating agent and catalytic amounts of 4-pyrrolidinylpyridine were stirred in CH_2Cl_2 until TLC showed complete conversion of **56** to a less polar product representing the activated adduct.[56,57] Only then, a solution of alcohol **36** in the minimum amount of CH_2Cl_2 was introduced[57] before most of the solvent was removed by a stream of argon and stirring of the essentially neat, viscous mixture was continued overnight. This protocol was



Scheme 10. a) EDC·HCl, 4-pyrrolidinylpyridine (12 mol%), CH_2Cl_2, 0°C, then **36**, 82%; b) **58** (10 mol%), toluene, 50°C, 72%; c) TBAF, THF, 0°C, 99%.

found reliable, providing good amounts of the metathesis precursor **57** (1.17 g, single largest batch).

In contrast to performing the ring-closing metathesis of polyene **57** in CH_2Cl_2 at ambient temperature as described in our first total synthesis,[10,11b] it was found beneficial to run the reaction in toluene[58] at 50°C under a constant stream of argon; a concentration of 10^{-3} M was found optimal. This set-up allowed the catalyst loading to be reduced from 20 mol% (in two portions) to 10 mol% (lower amounts of **58**[59,60] gave similar results, but incomplete conversion was noticed in a few runs). After quenching of the catalyst with ethyl vinyl ether and evaporation of the solvent, the crude metathesis product was purified by flash chromatography on silica; the addition of 1 mol% of Et_3N to the hexane/EtOAc eluent rendered the isolation much easier and gave analytically pure macrocycle **59** in yields that consistently exceeded 70% as a single isomer (only traces of the corresponding *Z* isomer were detected in the crude product). Even though the largest batches used no more than 300 mg of the metathesis precursor **57**, we have no reason to believe that the reaction would not work similarly well with larger amounts of material. Even though the power of RCM nowadays needs no further demonstration and has become common knowledge,[16] we do consider the closure of the 24-membered polyene **59** by selective activation of two out of ten double bonds as a triumph of the ruthenium carbene complexes developed by Grubbs[61] and as a highlight of our own work in the area of metathesis-based macrocyclization reactions.[62,63]

The final cleavage of the TBS group on the serine residue in **59** was essentially quantitative with TBAF in THF at 0°C. Utilizing this route, we were able to prepare slightly more than one gram of iejimalide B (**2**). Suffice it to say that the analytical and spectral data of this material matched those of the samples previously prepared in this laboratory[10] as well as those reported in the literature for the natural product in all regards.[1,2]

Conclusion

The gram-scale total synthesis of the marine natural product iejimalide B was accomplished in no more than 16 steps in the longest linear sequence (7% overall yield, 41 steps total). This closes the supply problem which had precluded a serious (pre)clinical evaluation of this promising anticancer agent for more than two decades. Moreover, this endeavor laid the ground for an extensive synthesis-driven mapping of the pharmacophore of this macrolide, which led to a representative collection of fully synthetic analogues of the natural lead.[13] Importantly, several of these "iejimalide-like" compounds are similarly potent but significantly more selective toward a panel of human tumor cell lines. Details of this work in the realm of "diverted total synthesis"[64,65] are outlined in the accompanying paper.[13]

Experimental Section

The entire Experimental Section, including compound characterization data, can be found in the Supporting Information.

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